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Review

Human metabolism of phytanic acid and pristanic acid

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Abstract

Phytanic acid is a methyl-branched fatty acid present in the human diet. Due to its structure, degradation by β-oxidation is impossible. Instead, phytanic acid is oxidized by α-oxidation, yielding pristanic acid. Despite many efforts to elucidate the α-oxidation pathway, it remained unknown for more than 30 years. In recent years, the mechanism of α-oxidation as well as the enzymes involved in the process have been elucidated. The process was found to involve activation, followed by hydroxylase, lyase and dehydrogenase reactions. Part, if not all of the reactions were found to take place in peroxisomes. The final product of phytanic acid α-oxidation is pristanic acid. This fatty acid is degraded by peroxisomal β-oxidation. After 3 steps of β-oxidation in the peroxisome, the product is esterified to carnitine and shuttled to the mitochondrion for further oxidation. Several inborn errors with one or more deficiencies in the phytanic acid and pristanic degradation have been described. The clinical expressions of these disorders are heterogeneus, and vary between severe neonatal and often fatal symptoms and milder syndromes with late onset. Biochemically, these disorders are characterized by accumulation of phytanic and/or pristanic acid in tissues and body fluids. Several of the inborn errors involoving phytanic acid and/or pristanic acid metabolism have been characterized on the molecular level.

Contents

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1. Phytanic acid and pristanic acid: introduction

Phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) is derived from phytol, the side chain of chlorophyll [1]. Absorption of chlorophyll in the human digestive tract is minimal [2]. Micro-organisms, present in the gastrointestinal system of ruminants, effectively release phytol from chlorophyll, after which phytol is converted into phytanic acid [3]. Phytanic acid in the human body is mainly derived from dairy products and ruminant fats. A normal diet contains 50–100 mg of phytanic acid per day [4].

The mechanism of phytanic acid degradation has long remained unknown. The β-methyl group in the phytanic acid molecule prevents degradation by β-oxidation, as formation of a 3-ketoacyl-CoA intermediate is impossible. Already in 1966 it was shown in mice that phytanic acid was subject to one cycle of α-oxidation, yielding pristanic acid (2,6,10,14-tetramethylpentadecanoic acid) [5]. Only recently, more than 30 years later, the exact mechanism and the enzymes of the α-oxidation pathway have been unravelled.

Pristanic acid was described for the first time in 1964, when it was isolated from butter fat and identified by mass spectrometry [6]. It was named after pristane (2,6,10,14-tetramethylpentadecane), a hydrocarbon isolated from shark liver (Latin: pristis) [7]. Pristanic acid, like phytanic acid, is present in lipids from many sources like krill, earthworms, whales, fish, human milk fat and bovine depot fat [8].

Phytanic acid and pristanic acid have three asymmetric centres. In phytanic acid, the methyl groups at carbons 7 and 11 are in the R configuration, as they are in phytol. The configuration at carbon 3 can be R or S, and the relative proportions of 3R and 3S phytanic acid in natural sources vary widely [9]. Both stereo-isomers of phytanic acid can be degraded by α-oxidation, resulting in two stereo-isomers of pristanic acid [9].

2. Phytanic acid α-oxidation

For a long time it was thought that, in contrast to straight-chain fatty acids, phytanic acid was degraded as a free acid [10–12]. However, in 1994, Watkins and colleagues provided convincing evidence that phytanic acid is first activated to phytanoyl-CoA [13]. The activating enzyme has not been fully identified, but it is localized on the cytoplasmic side of the peroxisomal membrane [13,14]. The reaction requires, like other acyl-CoA forming reactions, CoA, ATP and Mg^{2+}.

Phytanoyl-CoA enters the peroxisome by an unknown mechanism. Presumably, a membrane protein is responsible for active transport. Carnitine does not seem to be involved in peroxisomal import of CoA esters, as neither phytanoyl-carnitine nor pristanoyl-carnitine formation was found after incubation of fibroblasts with phytanic acid and/or pristanic acid [15].

Once inside the peroxisome, phytanoyl-CoA is converted into 2-hydroxyphytanoyl-CoA by phytanoyl-CoA hydroxylase (PhyH) [16–18]. This enzyme is an intermolecular dioxygenase, incorporating oxygen into each of two separate products: the substrate phytanoyl-CoA and the cosubstrate α-ketoglutarate [16–18]. As a result, 2-hydroxyphytanoyl-CoA and succinate are formed (Fig. 1). PhyH activity depends on the presence of iron (Fe^{2+}) and a reducing substance like ascorbate. PhyH has been purified from rat liver. The full length human cDNA has been cloned and sequenced [19,20]. It contains a cleavable peroxisome targeting sequence, PTSII, in line with the peroxisomal localisation of the hydroxylation reaction (Table 1).

Analogous to β-oxidation, the next step of α-oxidation could be formation of 2-ketophytanoyl-CoA, followed by carbon-carbon cleavage yielding pristanoyl-CoA. Extensive studies were aimed at the detection of 2-ketophytanic acid in blood and formation of this compound in vitro. Although never detectable in blood, formation of 2-ketophytanic acid was observed after incubation of human liver homogenates with 2-hydroxyphytanic acid [21,22]. However, when incubating with 2-hydroxyphytanoyl-CoA, the true α-oxidation intermediate, 2-ketophytanic acid formation was negligible. Therefore, the formation of 2-ketophytanic acid was considered an in vitro artefact [23].

A break-through in the elucidation of the mechanism of the carbon-carbon cleavage was the observation that not CO_2 but formate was the primarily released compound in the α-oxidation process, as was shown both in vitro as in vivo [18,24,25]. Further studies showed that first formyl-CoA is generated in the carbon-carbon cleavage, which is enzymatically converted to formate, and further metabolised to CO_2 in the cytosol [26]. In addition, studies in human liver homogenates showed that free pristanic acid was formed, and not pristanoyl-CoA [23]. The combination of these findings resulted in the discovery of the fatty aldehyde pristanal as product of the decarboxylation of 2-hydroxyphytanoyl-CoA [27,28]. The reaction is catalysed by 2-hydroxyphytanoyl-lyase (HPL). Activity of HPL is dependent on Mg^{2+} and thiamine pyrophosphate. The C-terminus of the lyase represents a PTS1 variant, which confines the enzyme reaction to the peroxisome [29]. However, activity of the lyase has also been found in the ER, for which no explanation is available at present [23,30].

No agreement on the last step, converting pristanal into pristanic acid, has been reached yet. Studies comparing fibroblasts from patients deficient in the microsomal fatty aldehyde dehydrogenase (FALDH) with control cells showed a reduced oxidation of phytanic acid in the FALDH-deficient cells. Recombinant human FALDH expressed in Chinese hamster ovary cells showed a severe deficiency in FALDH when pristanal was used as substrate [31]. These results indicate that the microsomal FALDH is involved in the phytanic acid α-oxidation pathway. However, microsomal localisation of the conversion of pristanal to pristanic acid would imply that pristanal, a potentially toxic compound, is exported from the peroxisome to the endoplasmic reticulum. After conversion of pristanal the resulting pristanic acid would have to re-enter the peroxisome for degradation by β-oxidation (Fig. 2). In isolated rat liver peroxisomes, the conversion of 2-methylpentadecanal, a model compound for pristanal, into 2-methylpentradecanoic acid has been observed [26]. This indicates that peroxisomes do also contain a fatty aldehyde dehydrogenase capable of converting pristanal, at least in rat.

3. Pristanic acid β-oxidation

3.1. The first cycle of pristanic acid β-oxidation

Prior to β-oxidation, pristanic acid is activated to pristanoyl-CoA. The enzymes responsible for this reaction have not been fully identified. Pristanic acid in the body is derived from two sources:

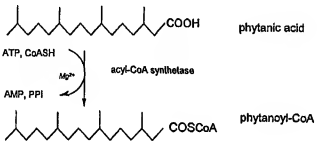

Fig. 1. Phytanic acid α-oxidation. For details see text.

the diet and production from phytanic acid by α-oxidation. For activation of pristanic acid from the diet, an enzyme located outside of the peroxisome is required. Long-chain acyl-CoA synthetase, which is facing the cytosol, is capable of activating pristanic acid to pristanoyl-CoA and might be involved in activation of diet-derived pristanic acid [32]. The localisation of pristanic acid formation from pristanal is not clear yet, both peroxisomes and ER having been mentioned in literature. When pristanic acid is formed within the peroxisome, intraperoxisomal activation seems most efficient. Very long-chain acyl-CoA synthetase (VLCS) is present in endoplasmic

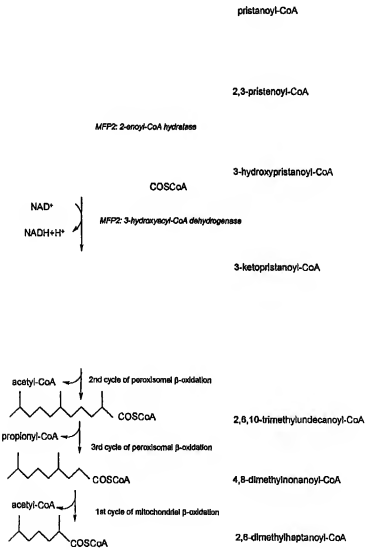

Fig. 2. Pristanic acid β-oxidation. For details see text.

Table 1
Enzymes involved in the α-oxidation of phytanic acid and the peroxisomal β-oxidation of pristanic acid and the deficiencies of these enzymes in peroxisomal disorders[a]

Enzyme	Cofactors	Cellular localisation	pts	Mol weight	chromosome	Deficient in	Ref.
Phytanoyl-CoA synthetase or Long-chain acyl-CoA synthetase	ATP, Mg^{2+}, CoA	Mitochondrion, peroxisome, ER			n.a.		[13,14]
Phytanoyl-CoA hydroxylase	Fe^{2+}, ascorbate, α-ketoglutarate	Peroxisome	Pts2	41.2 kDa	10	RD, RCDP, PBD	[17]
2-Hydroxyphytanoyl-CoA lyase	Mg^{2+}, thiamine	Peroxisome, ER	Pts1v	63.7 kDa	n.a.		[29,30]
Fatty aldehyde dehydrogenase	$NAD(P)^+$	Er			n.a.		[31]
Long-chain acyl-CoA oxidase and very long-chain acyl-CoA oxidase	ATP, Mg^{2+}, CoA	Peroxisome			n.a		[32,33]
α-Methyl-CoA racemase	–	Peroxisome, mitochondrion	Pts1v	43.3 kDa	n.a.	AMCAR deficiency	[34–36]
Branched-chain acyl-CoA oxidase	FAD	Peroxisome	Pts1	47 kDa	3p14.3		[37-38]
MFP2: 2-enoyl-CoA hydratase		Peroxisome	Pts1	77 kDa	5q2.3	MFP2, PBD?	[39–42]
MFP2: 3-hydroxyacyl-CoA dehydrogenase	NAD+	Peroxisome	Pts1	80 kDa			[39–42]
SCPx	CoA	Peroxisome	Pts1	58 kDa	n.a.		[45]

[a] RD, Refsum diseasel Pts, peroxisomal targetting sequence; Pts1v, peroxisomal targetting sequence type I variant; n.a., information not available; ER, endoplasmic reticulum.

reticulum and in the peroxisomal membrane, where it faces the peroxisomal matrix. It has activity to very long-chain fatty acids and also to long-chain fatty acids, phytanic acid and pristanic acid. It was postulated that it is involved in the activation of pristanic acid that is peroxisomally produced during phytanic acid metabolism [33].

As only the stereoisomer with the 2-methyl group in the S-configuration can be degraded by β-oxidation, 2R-pristanic acid needs to be racemized prior to its degradation [34]. α-Methyl-CoA racemase (AMCAR) catalyses the conversion of several (2R)-methyl-branched-chain acyl-CoAs to the corresponding S-stereoisomers [35,36]. AMCAR is present in the peroxisome and in the mitochondrion. As both activities are derived from the same gene, the bimodal distribution pattern must be the result of differential targeting of the same gene product [36].

The first step of β-oxidation, desaturation of pristanoyl-CoA to form 2,3-pristenoyl-CoA is catalysed by branched-chain acyl-CoA oxidase (BRCAox), one of the two acyl-CoA oxidases present in human peroxisomes [37,38]. This enzyme is active on 2-methyl-branched compounds like pristanic acid and trihydroxycoprostanoyl-CoA, but also on straight-chain acyl-CoAs. The other acyl-CoA oxidase, also called palmitoyl-CoA oxidase, is active on straight-chain mono- and dicarboxylic acids only. Peroxisomal desaturation is FAD-dependent and molecular oxygen is reduced to form hydrogen peroxide, which is rapidly decomposed by catalase.

The next two steps of β-oxidation are catalysed by a multifunctional protein, harbouring 2-enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase activities. For a long time it was thought that peroxisomes contain only one multifunctional enzyme, which was involved in β-oxidation of all substrates. Studies in rat and human liver peroxisomes, however, revealed the presence of another multifunctional protein, which was named multifunctional protein 2 (MFP-2) [39–42]. The first MFP (MFP-1) was found to form and convert L-3-hydroxyacyl-CoA compounds, whereas MFP-2 catabolises the D-configuration of its substrates. Degradation of 2,3-pristenoyl-CoA involves MFP-2 (now also called D-bifunctional protein). This enzyme is a multidomain protein, the N-terminal domain containing a 3-hydroxyacyl-CoA dehydrogenase domain, the central part possessing enoyl-CoA dehydrogenase activity and the C-terminal showing homology to sterol carrier protein-2 [43]. β-oxidation of very long-chain fatty acids and bile acid intermediates also involves MFP-2. The role of MFP-1 is not known.

The last step of the β-oxidation cycle is thiolytic cleavage of the substrate, catalysed by 3-ketoacyl-CoA thiolase. The presence of thiolase in peroxisomes was reported in the early 1980s by Hashimoto and colleagues [44]. More recently, it was found that SCPx, a 58 kDa protein, has thiolase activity [45]. Probably, after peroxisomal import, the 58 kDa protein is proteolitically cleaved to produce a 46 kDa thiolase and a 123 amino acid sterol carrier protein. SCPx is involved in the degradation of branched-chain substrates, whereas straight-chain acyl-CoA esters are converted by 3-ketoacyl-CoA thiolase.

3.2. Complete degradation of pristanic acid

The product formed after one cycle of peroxisomal β-oxidation of pristanic acid is 4,8,12 trimethyltridecanoyl-CoA (Fig. 2). This compound has a methyl group in the 4 position and is further degraded by peroxisomal β-oxidation. Whether the same enzymes are involved in breakdown of the 4-methyl compound as in the first cycle has not been established. The product of the second cycle is a 2R-methyl-branched acyl-CoA, 2,6,10-trimethylundecanoyl-CoA. Before this

intermediate can be degraded, it needs to be converted into the 2S stereoisomer, presumably by AMCAR [36].

In successive cycles of β-oxidation, propionyl-CoA and acetyl-CoA are alternately released. Propionyl-CoA is converted into propionyl-carnitine within the peroxisomal matrix, after which it is transported to the mitochondrion, where it is oxidised to CO_2 [46]. The fate of the acetyl units generated in the peroxisomal β-oxidation process is not clear. It may be used for fatty acid biosynthesis or enter the mitochondrion as acetylcarnitine.

Peroxisomal β-oxidation of pristanic acid is limited and does not go to completion. The factor that limits β-oxidation is not known, but probably the substrate specificity of branched-chain acyl-CoA oxidase is an important factor.

After three cycles of peroxisomal β-oxidation, 4,8-dimethylnonanoyl-CoA results, as was shown in experiments in which fibroblasts in culture were incubated with pristanic acid [47]. Using cells with deficiencies of carnitine palmitoyl-transferase I (CPTI), carnitine acylcarnitine carrier (CAC) and carnitine palmitoyltransferase II (CPTII) and cells from a patient affected with

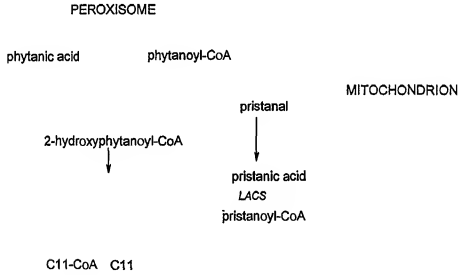

Fig. 3. Model of the functional and physical organisation of phytanic acid and pristanic acid oxidation in human fibroblasts. COT, carnitine octanoyltransferase; LACS, long-chain acyl-CoA synthetase; CAC, carnitine acylcarnitine carrier; CPTI, carnitine palmitoyltransferase I; CPT II, carnitine palmitoyltransferase II; IM, inner mitochondrial membrane; OM, outer mitochondrial membrane.

Zellweger syndrome, lacking peroxisomes, the fate of 4,8-dimethylnonanoyl-CoA was elucidated. It was shown that 4,8-dimethylnonanoyl-CoA is converted into its carnitine ester within the peroxisome by carnitine octanoyltransferase [48]. Hereafter, it is exported to the mitochondrion and imported into the mitochondrion by CAC and CPTII. In the mitochondrion, 4,8-dimethylnonanoyl-CoA is degraded to 2,6-dimethylheptanoyl-CoA. This latter compound has a 2R-methyl group. As acyl-CoA dehydrogenases are specific for 2S-compounds, 2,6-dimethylheptanoyl-CoA first has to be racemized. It was recently shown that this racemisation is catalysed by AMCAR, which is not only localized in peroxisomes but also in mitochondria. Further mitochondrial β-oxidation of 2,6-dimethylheptanoyl-CoA involves long-chain acyl-CoA dehydrogenase [49].

4. Inherited defects in the degradation of phytanic acid and pristanic acid

4.1. Isolated peroxisomal enzyme deficiencies

4.1.1. Classical Refsum disease

Refsum disease was first described as a familial clinical syndrome, heredopathia atactica polyneuritiformis [50]. Consistent clinical findings are pigmentary retinal degeneration, peripheral neuropathy, cerebellar ataxia and high concentrations of protein in the cerebrospinal fluid. Other frequently observed abnormalities are cardiomyopathy, ichthiosis-like skin problems, skeletal abnormalities of hands and feet, anosmia and sensorineural deafness. The age of onset of clinical symptoms varies from early childhood to the sixth decade, but in most patients the disease becomes manifest at teenage or young adult age. The course of the disease is one of gradual progression often interrupted by unexplained periods of remission. Sudden death has been described several times. Refsum disease is very rare, not more than 150 patients have been diagnosed world wide [51].

The biochemical hallmark of Refsum disease is an impressing accumulation of phytanic acid in blood and tissues. The concentration of phytanic acid in plasma may become as high as 1300 μmol/l (controls <10 μmol/l) [52]. Pristanic acid concentrations are normal. The accumulation of phytanic acid is caused by a deficiency of PhyH, the first enzyme of the α-oxidation process [19,20]. Activity measurements of PhyH in liver and fibroblasts from patients have shown a deficiency of this enzyme in all patients investigated. Distinct mutations in the PhyH cDNA have been found, which confirmed the enzyme analyses. Recent studies using linkage analysis reported genetic heterogeneity in Refsum disease. In three out of seven families linkage to the PhyH gene locus was excluded, which led the authors to state that Refsum disease is a heterogeneous syndrome. Unfortunately, the patients which were subjects in this study were diagnosed on the basis of clinical symptoms and plasma phytanic acid concentrations only, and no enzyme activities of PhyH were presented [53].

4.1.2. α-methylacyl-CoA racemase deficiency

Recently, deficiency of the peroxisomal α-methylacyl-CoA racemase was reported [54]. Two of the three affected patients suffered from adult onset sensory motor neuropathy. One of them also had pigmentary retinopathy, whereas the other patient had upper motor neurone signs in the legs.

The third patient was a child without neuropathy. Biochemically, all three patients had marked increases of plasma pristanic acid and bile acid intermediates and only mild elevations of phytanic acid. Very long-chain fatty acid concentrations were within the reference ranges, ruling out a peroxisome biogenesis defect. The combination of findings suggested a specific defect in the peroxisomal degradation of branched-chain fatty acids. Pristanic acid β-oxidation was found to be deficient in cultured fibroblasts. However, the individual enzymes involved in degradation of pristanic acid, branched-chain acyl-CoA oxidase, MFP2 and SCPX all had normal activities. Investigation of α-methylacyl-CoA racemase (AMCAR) showed a complete deficiency of this enzyme in all three patients. Sequencing of the AMCAR cDNA revealed mutations. These mutations were found to result in loss of activity of the enzyme as shown by expression studies in *E. coli*.

The full clinical spectrum of this newly discovered disease is not yet known. The similarity in symptoms of AMCAR deficiency and classical Refsum disease suggests that elevated levels of branched-chain fatty acids result in adult-onset neuropathy. Treatment of AMCAR deficiency by restricting the amount of phytanic acid and pristanic acid in the diet, as in Refsum disease, may improve the clinical symptoms.

4.1.3. Multifunctional protein type II deficiency

The existence of a second peroxisomal multifunctional protein was discovered only recently. Until then, it was thought that both branched-chain as well as straight-chain substrates were degraded by one single peroxisomal β-oxidation system. The description of a patient with accumulation of very long-chain fatty acids, bile acid intermediates and pristanic acid and an absence of bifunctional protein on immunoblot was in line with the concept of one β-oxidation system in peroxisomes [55]. Recent investigations in the cells of this patient have shown a two base pair deletion resulting in a truncated protein in the MFP2 cDNA, whereas no mutations in the gene for MFP1 were found [56]. This was a surprising finding, as the MFP which was originally found absent in the patient is now known as MFP1, and no explanation for this discrepancy has been found.

In addition, several more patients originally diagnosed with bifunctional protein deficiency have been characterised on the molecular level. In all of these patients mutations or deletions in MFP2 were found [57].

Clinically, MFP2 deficiency resembles a PBD, with dysmorphic features, severe central nervous system involvement, seizures and failure to acquire any significant developmental milestones. Most patients accumulate straight-chain fatty acids (very long-chain fatty acids), and branched-chain compounds (pristanic acid, bile acid intermediates). The cause of this combination is mysterious and it suggests that D-MFP2 is involved in degradation of both groups of compounds. Indeed, when fibroblasts of a patient lacking MFP2 were incubated with radiolabelled pristanic acid, C26:0 and bile acid intermediates, no oxidation of any of these substrates was found [58]. These results imply that MFP2 is involved in oxidation of branched-chain as well as straight-chain substrates. The role of MFP1 remains to be established.

The β-oxidation intermediates of pristanic acid: 2,3-pristenic acid and 3-hydroxypristanic acid, were found to be increased in plasma from nine patients affected with BP deficiency. The high levels of both intermediates pointed to an intact formation of 3-hydroxypristanoyl-CoA, and thus suggested intact activity of the hydratase domain of MFP2 in all these patients [58].

4.1.4. Peroxisomal thiolase deficiency

Only one patient affected with peroxisomal β-ketothiolase deficiency has been reported [59,60]. The clinical symptoms resemble those of Zellweger syndrome, including the typical dysmorphia. Bile acid intermediates and very long-chain fatty acids were elevated in blood and immunoblotting showed absence of peroxisomal 3-ketoacyl-CoA thiolase. The other peroxisomal β-oxidation enzymes were normally present. Peroxisomes were present in liver, but enlarged. Unfortunately, phytanic acid and pristanic acid levels in blood were not reported and fibroblasts of this patient are no longer available.

4.2. Peroxisome biogenesis defects

The peroxisome biogenesis defects (PBD) are a group of disorders with different genetic causes [see 61 for overview]. Despite genetic heterogeneity, they have the absence of functional peroxisomes in common. The absence of peroxisomes results in a range of biochemical abnormalities and variable clinical symptoms. The most severe clinical phenotype, the Zellweger syndrome, is a polymalformation condition, affecting the development of brain, liver, kidney and skeleton. Affected patients have severe neurological and hepatic dysfunction, a typical facial appearance and usually die within the first year of life. On the other hand, PBD can manifest milder symptoms, like psychomotor retardation, mild neurological dysfunction and a life expectancy of more than 10 years.

The underlying defects in all PBD are deficiencies in the import of peroxisomal matrix proteins. To date, more than 12 complementation groups are known. Patients with the same genotype may present with different clinical phenotype, whereas patients with similar phenotypes may have different genotypes.

In plasma from patients suffering from a defect in peroxisome biogenesis, elevated concentrations of phytanic acid and pristanic acid are found [62]. PhyH is deficient in liver and in fibroblasts, which is in line with the observation that PhyH is a peroxisomal matrix protein. Often, there is some residual activity of PhyH, as was shown by in vitro experiments using fibroblasts from PBD patients [63]. The residual activity of PhyH may also explain the presence of 2-hydroxyphytanic acid in plasma from affected patients [64].

The second enzyme of the α-oxidation pathway, phytanoyl-CoA lyase, shows a normal activity in livers from patients affected with Zellweger syndrome [65]. This observation can be explained in two different ways. One possibility is that 2-hydroxyphytanoyl-CoA lyase is stable and thus active in the cytosol. This phenomenon has been observed for other enzymes as well, for example for catalase and glyoxylate aminotransferase. The other explanation for the normal activity of the lyase in ZS liver could be the presence of HPL in the endoplasmic reticulum, as was recently described [30]. This is also in line with earlier observations that 2-hydroxyphytanoyl-CoA can be converted into pristanic acid in livers from patients affected with Zellweger syndrome [23]. This latter observation also suggests that the aldehyde dehydrogenase, which converts pristanal into pristanic acid, is not affected in PBD. Pristanic acid β-oxidaton is impaired, explaining the elevated concentrations of pristanic acid in plasma from affected patients. Small amounts of pristanic acid β-oxidation intermediates are present in plasma from PBD patients, suggesting residual activity of the β-oxidation enzymes. In a recent paper by Ferdinandusse et al. it was shown that SCPx is stable in the cytosol of peroxisome deficient cells [66]. A surprising finding

was that the activity of SCPx in fibroblasts from PBD patients was higher than in control fibroblasts [66].

Next to accumulation of phytanic acid and pristanic acid, elevated concentrations of very long-chain fatty acids, pipecolic acid and bile acid intermediates are found in plasma from patients affected with a PBD.

Rhizomelic chondrodysplasia punctata is a PBD which results from a genetic defect in the PTS2 receptor encoded by the HsPEX7 gene [67–69]. In patients suffering from RCDP type I, phytanic acid accumulates due to a deficiency of PhyH [70]. This deficiency probably results from a mislocalisation of PhyH, a PTS2 protein, as a consequence of the non-functional PTS2 receptor. Hydroxyphytanoyl-CoA lyase, the next enzyme of the α-oxidative pathway, probably has normal activity, as it is a PTS1 protein. Whether or not the aldehyde dehydrogenase is deficient is not known. The peroxisomal β-oxidation pathway is fully active in patients affected with RCDP.

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